REMARKS

Claims 37-46 were previously pending in this application. By this amendment, claims 37, 39, 41 and 46 have been amended, claims 38 and 40 have been canceled, claim 47-55 have been withdrawn, and new claim 55 has been added. As a result claims 37, 39, 41-46 and 55 are pending for examination with claim 37 being independent claim. Support for the amendments to the specification and claims are supported by the specification as filed.

The subject matter of canceled claims 38 and 40 has been incorporated into claim 37.

Claim 46 has been amended to correct an error in its dependency and to take account of a lack of antecedent basis for the reference to "the vaccine" in the old form of the claim. In addition, Applicant has replaced the requirement in the old claim that "both" FHA and P69 are used with wording that makes clear that each antigen may be used individually. Support for the amended claim is found, for example, at page 7, fourth full paragraph.

New claim 55 specifies that both FHA and P69 are used.

No new matter has been added.

Priority

As regards paragraph 2 of the Office Action, the instant application has already been amended to refer to previously filed related applications by way of a Preliminary Amendment filed on February 2, 2001. The Related Application section has been amended herewith to indicate that the parent application is now abandoned.

As regards paragraph 3 of the Office Action, Applicant points out that the instant application is derived, via the filing of two US continuation applications, from a PCT application. The GB priority applications should therefore have been provided to the USPTO by the International Bureau under Rule 17.2 PCT in the first US application in the family. The United Kingdom Patent Office is unable to provide further photocopies of certified copies of the priority applications because the applications were abandoned long ago in favour of the PCT application and the Patent Office has destroyed its files. However, for the convenience of the Examiner, Applicant has provided herewith certified copies of the two GB applications.

Specification

As regards paragraph 5 of the Office Action, the title has been amended as requested by the Examiner.

As regards paragraph 6 of the Office Action, the Examiner's attention is drawn to the fact that an abstract on a separate sheet was submitted with the Preliminary Amendment of February 2, 2001. If the Examiner requires a copy of the abstract, then Applicant requests that the Examiner indicate so in any subsequent Office Action.

As regards item 7 of the Office Action, Applicant has amended the specification to take account of the preferred arrangement set forth by the Examiner.

Oath/Declaration

A new Declaration is attached.

Information Disclosure Statements

Applicant thanks the Examiner for initialling and returning the information disclosure statement (IDS) submitted on October 2, 2002.

However, Applicant notes that the Examiner has not initialled and returned an IDS filed on February 2, 2001. Please would the Examiner initial and return that IDS.

Claim Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 37, 38, 40 and 42-44 under 35 U.S.C. § 102 as anticipated by Capiau *et al* (EP-A-0352250). Reconsideration of the rejection over Capiau is respectfully requested.

Capiau teaches a vaccine comprising pertussis toxin in which the S1 subunit contains a mutation at position 26 (abstract). Capiau also teaches that the S1 subunit may be a double mutant and that the second mutation may be at position Glu-129 or Arg-9 amongst other possible positions (page 6, lines 14-25).

However, Capiau does not teach a mutant in which both Glu-129 and Arg-9 are mutated as recited in the instant claims. The double mutant of Capiau contains a mutation at position Trp-26 as a first mutation, and only one other position can be mutated to produce the double

mutant. The other position can be either Glu-129 or Arg-9, but it cannot be both. The instant claims are therefore novel over Capiau.

Claim Rejections Under 35 U.S.C. § 103

The Examiner rejected claims 37-44 and 46 under 35 U.S.C. § 103(a) as unpatentable over Nencioni *et al* and Podda *et al* in view of Capiau *et al*, Tamura *et al* and Honda *et al*. Reconsideration of the rejection of claims 37-44 and 46 under 35 USC § 103 and the separate rejection of claim 45 under 35 U.S.C. § 103(a) is requested.

As noted by the Examiner, the primary references, Nencioni *et al* and Podda *et al*, do not teach administering the double mutant toxin and antigen in the form or nasal drops or nasal spray for mucosal administration. For reasons given below, Applicant submits that it would not have been obvious to a person of ordinary skill in the art to administer the double mutant toxin described in Nencioni *et al* and Podda *et al* by a mucosal route in a method of stimulating or enhancing a protective immune response to an antigen.

Applicant believes that the claimed invention was not obvious for essentially three reasons. Firstly, it would not have been obvious to combine either or the primary references, Nencioni *et al* and Podda *et al*, with the secondary references, Capiau *et al*, Tamura *et al* and Honda *et al*. Secondly, even if a skilled person had combined the references, it would not have been obvious from the combined teachings that the double mutant toxin recited in the claims would stimulate or enhance a protective immune response to an antigen when administered by a mucosal route. Thirdly, the claimed method is unexpectedly effective; the double mutant toxin recited in the claims is unexpectedly highly effective as an adjuvant when administered by a mucosal route. Applicant will explain each of these three reasons for non-obviousness in detail below.

It is well established in the case law that the test for obviousness over a combination of references should involve a consideration of whether it was obvious to make the combination in the first place. The USPTO's Manual of Patent Examining Procedure repeatedly makes this clear. In particular, the Manual states that:

> "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine reference teachings. The Federal Circuit has produced

> a number of decisions overturning obviousness rejections due to a lack of suggestion in the prior art of the desirability of combining references" (MPEP 2145).
>
> "Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly of implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art" (MPEP 2143.01).
>
> "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination" (MPEP 2143.01).
>
> "The combination of the references taught every element of the claimed invention, however without a motivation to combine, a rejection based on a prima facie case of obviousness was held improper" (MPEP 2143.01).

In the instant case, Applicant submits that there was no obvious motivation to combine the references cited by the Examiner. There were a vast number of publications in the art on pertussis toxin; a recent search for publications containing the term "pertussis toxin" in the title on PubMed produces 1815 references, 1205 of which were published before the first GB priority date in October 1993.

There is no obvious reason why a skilled person would have picked the references cited by the Examiner out of this vast amount of prior art references and held them in the forefront of his/her mind at the same time. Applicant reminds the Examiner that the cited references have necessarily been selected with the benefit of knowledge of the instant invention, i.e. with the benefit of hindsight. In view of the large number of references in this field of art, it appears that it is the knowledge of the instant invention that motivated the Examiner to put the references together. A skilled person working before the date of invention would not have had the benefit of this hindsight knowledge and, accordingly, would not have had the motivation to make the combination made by the Examiner.

A major reason why the Examiner has chosen to cite the three secondary references, Capiau *et al*, Tamura *et al* and Honda *et al*, is that they disclose mucosal administration. However, it must be borne in mind that, at the date of invention, mucosal routes of administration were not conventional for vaccines and a skilled person would not ordinarily have focussed on documents relating to mucosal administration. Evidence for this is provided by Honda, which states in the last paragraph on page 1 that:

> "Many enzymes are used with the object of preventing infectious diseases, but with the exception of a small number of cases, such as with the oral administration of polio

vaccines, administration is almost always carried out by a subcutaneous route." (Emphasis added.)

The reason that mucosal administration was not normal was that, as set out in the description of the background art in the specification, most non-replicating immunogens are poorly immunogenic when ingested or inhaled, and soluble proteins are particularly inefficient mucosal immunogens. This is because the non-specific defenses of the mucosa will readily denature, degrade and eliminate most proteins, resulting in the mucosa-associated lymphoid tissue (MALT) encountering only minute quantities of such immunogens. As a consequence, it is notoriously difficult to predict whether a given antigen will exhibit immunogenic activity when administered by the mucosal route, for example by intranasal administration.

The references cited by the Examiner do not suggest sufficient advantages of the mucosal route to motivate a skilled person to use that route instead of the conventional routes.

Capiau merely lists "oral" and "intranasal" administration in a throw-away sentences containing standard lists of routes of administration (page 7, lines 55-57 and page 8, lines 47-49). Capiau does not suggest that there is any special advantage in using the oral or intranasal route. On the contrary, Capiau teaches that other routes are preferred; Capiau teaches that its vaccine is "preferably administered parenterally via the intramuscular or deep subcutaneous routes" (page 7, lines 54-55). Applicant therefore submits that Capiau teaches away from the instantly claimed invention, and that any suggestion that Capiau would have helped to motivate a skilled person to dispense with the conventional routes of administration, and switch to a mucosal route, is unfounded.

Tamura in fact clearly teaches away from attempting to use pertussis toxin as an adjuvant by delivering it by the intranasal route; the data in the Examples of Tamura teach that pertussis toxin is a poor adjuvant. For example, the results presented in Example 14 of Tamura show that, when a pertussis vaccine comprising both pertussis toxin and FHA was administered alone, the resulting antibody titre against both the pertussis toxin (PT) and FHA was very low; see the last line of results in the first table in column 18. It was only when LT or LTB was added that any significant adjuvant effect was observed.

The Examiner argues that Tamura teaches that nasal administration has the benefit of stimulating IgA production. However, the part of Tamura *et al* referred to by the Examiner (column 3) relates to administration of a flu antigen (HA antigen) together with cholera toxin

subunit B (CTB). That part of Tamura is of little relevance to the present invention because it teaches nothing whatsoever about the adjuvant properties of the double mutant pertussis toxin recited in the claims. As mentioned above, the data in Tamura relating to pertussis toxin suggests that it is a poor adjuvant when administered nasally.

Honda also teaches away from the instant invention. Pertussis toxin comprises two subunits, the A subunit (which is also called the S1 subunit) and the B subunit (which is in fact a composite of four polypeptides called S2, S3, S4 and S5). The instant invention requires the use of a double mutant form of the S1 subunit. In contrast, Honda specifically teaches that only the B subunit should be administered intranasally and that administration of the S1 subunit is to be avoided. See the paragraph bridging pages 2 and 3 of Honda, where the toxic properties of the A/S1 subunit are discussed and then it is stated that:

> "by using only sub-units which construct the B oligomer and have only cell affinity activity, or a composite of such sub-units, the activity of the original toxin will not be demonstrated, and there will only be realised an increase in the recognition towards the immune system of other antigens within the vaccine." (Emphasis added.)

According to the Reference Example on page 4 of Honda, the B subunit is purified in a manner designed to remove the S1/A subunit and the Example concludes by stating specifically that:

> "No sub-unit of proteins of A protomer were detected, and this sample just comprised the sub-unit proteins of the B oligomer."

In the art vaccines, it is notoriously difficult to predict whether a substance will function as an adjuvant, given that the precise manner in which adjuvants work is something of a mystery. The non-toxic double mutant of pertussis toxin recited in the claims is a highly effective adjuvant and is more effective than even the wild-type form of pertussis toxin. That could and would not have been predicted by a person of ordinary skill in the art before the date of invention.

The unexpected effectiveness of the instant invention is demonstrated in the Examples of the specification. For example, the Examples show that (pages 16 and 17):

> "Anti-fragment C antibodies were not detected in mice immunized I\N with ... Frg C + PTX [wild-type pertussis toxin]" but that "mice receiving Frg C combined with PT-9K/129G [the mutant toxin recited in the claims]...had significant amounts of anti-FrgC antibodies in their serum."

"Anti-PTX antibodies were present in mice receiving PT-9K/129G but not PTX"

"the boosted Frg C + PTX mice had developed circulating anti-PTX antibodies (Figure 6). However, both the anti-Frg C and anti-PTX response was considerably inferior to that of Frg C + PT-9K/129G mice (Figures 5 and 6)".

The Examples in the specification are confirmed by Roberts *et al* (1995) Infection and Immunity 63, 2100-2108. Roberts shows that (page 2104, left column):

"PT-9K/129K, which lacks ADP-ribosyltransferase activity, can greatly enhance the circulating and secretory antibodies to FrgC conadminsitered to the nasal cavaties of both inbred and outbred mice.... The adjuvant effect of PTX was more variable and depended on the source of the toxin."

Roberts concludes that (last sentence of the abstract):

"the pertussis toxin analog PT-9K/129G, which is devoid of ADP-ribosyltransferase activity, is a potent mucosal adjuvant for vaccines delivered via the respiratory tract."

The results shown in the Examples and in Roberts are the opposite of what would have been expected. The mutations at positions 9 and 129 recited in the claims are designed to destroy the toxic activity of the toxin. Applicant found that the mutations have the opposite effect on the ability of the toxin to induce an immune response, particularly an immune response that recognises the native form of the toxin. That was not obvious. Thus the application contained unexpected results that provide an additional basis for patentability and nonobviousness over the cited prior art.

In view of the foregoing amendments to the claims and arguments, Applicant respectfully requests that the rejection of claims 37-44 and 46 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, this application should now be in condition for allowance. A notice to this effect is respectfully requested. If the Examiner believes, after this amendment, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Mark Roberts, Applicant

John R. Van Amsterdam, Reg. No. 40,212
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210
Telephone: (617) 720-3500

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